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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/593,842	07/10/2007	Yusuke Nakamura	082368-000510US	3233

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EXAMINER	
WHITEMAN, BRIAN A	
ART UNIT	**PAPER NUMBER**
1635	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/593,842	NAKAMURA ET AL.	
	Examiner	Art Unit	
	Brian Whiteman	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 June 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-44,46-48,54-58 and 60-69* is/are pending in the application.

4a) Of the above claim(s) *1-43 and 62-68* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *44,46-48,54-57,60 and 69* is/are rejected.

7)☒ Claim(s) *58 and 61* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

This application contains claims 1-43 and 62-68 drawn to an invention nonelected with traverse in the reply filed on 11/26/08 and 1/12/09. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

Specification

The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code. Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01. For example, see pages 56 and 67.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 46, 47, 54-56, and 69 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The limitation 'wherein said KIF22 target sequence comprises a nucleotide sequence of SEQ ID NO: 34 and wherein the target sequence is from 19 to 25 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 1' in amended claims 46, 54-56, and new claim 69 is not supported by the as-filed specification. Applicant has cited parts of the application where the amended claims are supported, however, there does not appear to be a written description of the claim limitation 'wherein said KIF22 target sequence comprises a nucleotide sequence of SEQ ID NO: 34 and wherein the target sequence is from 19 to 25 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 1' in the application as filed. See MPEP § 2163.06. Applicants cite paragraphs [0272] and [0275] of the instant specification for support of the limitations.

Paragraphs [0272] recite:

The double-stranded molecule of the present invention comprises a sense strand and an antisense strand, wherein the sense strand comprises a ribonucleotide sequence corresponding to a KIFll, GHSRlb, NTSR1 or FOXM1 target sequence, and wherein the antisense strand comprises a ribonucleotide sequence which is complementary to said sense strand, wherein said sense strand and said antisense strand hybridize to each other to form said double-stranded molecule, and wherein said double-stranded molecule, when introduced into a cell expressing a KIF11, GHSRlb, NTSR1 or FOXM1 gene, inhibits expression of said gene.

Paragraph [0275] recites:

The double-stranded molecule of the present invention contains a ribonucleotide sequence corresponding to a KIF11, GHSRlb, NTSR1 or FOXM1 target sequence shorter than the whole mRNA ofKIF11, GHSRlb, NTSR1 or FOXM1 gene. Herein, the phrase a "target sequence of KIF11, GHSRlb, NTSR1 or FOXM1 gene" refers to a sequence that, when introduced into NSCLC cell lines, is effective for suppressing cell

viability. Specifically, the target sequence comprises at least about 10, or suitably about 19 to about 25 contiguous nucleotides from the nucleotide sequences selected from the group of SEQ ID NOs: 1, 3, 5, and 106. That is, the sense strand of the present double-stranded molecule consists of at least about 10 nucleotides, suitably is longer than 19 nucleotides, and more preferably longer than 21 nucleotides. Preferred target sequences include the sequences of SEQ ID NOs: 32, 33, 34, 35, 36, 37, and 108. The present double-stranded molecule including the sense strand and the antisense strand is an oligonucleotide shorter than about 100, preferably 75, more preferably 50 and most preferably 25 nucleotides in length. A suitable double-stranded molecule of the present invention is an oligonucleotide of a length of about 19 to about 25 nucleotides. Furthermore, in order to enhance the inhibition activity of the siRNA, nucleotide "u" can be added to 3'end of the antisense strand of the target sequence. The number of "u"s to be added is at least 2, generally 2 to 10, preferably 2 to 5. The added “u"s form single strand at the 3'end of the antisense strand of the siRNA. In these embodiments, the siRNA molecules of the invention are typically modified as described above for antisense molecules. Other modifications are also possible, for example, cholesterol-conjugated siRNAs have shown improved pharmacological properties (Song *et al. Nature Med.* 9:347-351 (2003):).

. The specification discloses the target sequence comprises at least about 10 nucleotides selected from the nucleotide sequence of SEQ ID NO: 1 **or** preferred target sequence includes the sequence of SEQ ID NO: 34. The specification does not disclose the subgenus set in the amended claims and claims dependent therefrom. Nothing in the specification would lead one of skill in the art to the particular combination set forth in the amended and claims dependent therefrom and new claims. "It is not sufficient for purposes of the written description requirement of Section 112 that the disclosure, when combined with the knowledge in the art, would lead one to speculate as to modifications that the inventor might have envisioned, but failed to

disclose." See *Lockwood v. American Airlines Inc.,* 41 USPQ2d 1961, 1966 (CAFC 1997).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 44, 46, 48, 54-56, 60, and 69 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wood et al. (US 6,414,121) taken with Tuschl (The siRNA user guide, 2001) in further view of Khvorova et al. (US 2007/0031844). Wood et al. teach antisense molecules targeting kinesin KSP and kinesin KSP being involved in cellular proliferation in cancer (abstract and columns 3-4). Wood et al. further teach a kinesin KSP nucleic acid comprising SEQ ID NO: 34 (SEQ ID NO: 7). However, Wood et al. do not specifically teach double stranded molecule comprising a nucleotide comprising at least 10 contiguous nucleotides from the nucleotide sequence of SEQ ID NO: 1. NOTE: SEQ ID NO: 1 comprises SEQ ID NO: 34.

Tuschl et al. teach a dsRNA design tool and guidelines for dsRNA design to generate a report indicating preferential sense and antisense dsRNA oligonucleotides for a given mRNA sequence. In addition, Khvorova et al. teach a method of producing and screening dsRNA molecules that successfully inhibit a target sequence (abstract and pages 96-99). Furthermore, Khvorova et al. teach that one of ordinary skill in the art using Tuschl's protocol would successfully produce dsRNA molecules that inhibits a target sequence (page 4 of provisional 60/502,050 cited on 20070031844).

It would have been obvious to utilize a dsRNA molecule, as taught by Wood, Khvorova, and Tuschl to study inhibition of kinesin KSP in cells and to design the dsRNA using the guidelines targeted to a kinesin KSP gene.

One of ordinary skill in the art would have been motivated to study kinesin KSP expression in cancer cells via inhibiting kinesin KSP with a dsRNA because Wood et al. teach the kinesin KSP nucleic acid and the up-regulation of this gene (columns 3-4) and

Khvorova teach that dsRNA molecules are preferential inhibitory molecules; achieve the product because Tuschl and Khvorova teach guidelines, wherein insertion of the kinesin KSP sequence taught by Wood et al. results in the identification of hotspots and preferential dsRNA sequences and specifically identified a sequence that is identical to a preferred sense strand of a dsRNA molecule.

"The combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results." See ***KSR v. Teleflex***, 550 U.S. ___, 127 S. Ct. 1727 (2007).

Since it was known that kinesin KSP expression is upregulated in cancer cells, as evidenced by Wood et al., one of ordinary skill in the art would have been motivated to study the inhibition of kinesin KSP expression. Furthermore, one of ordinary skill in the art would have been motivated to insert the known kinesin KSP sequence into publicly accessible siRNA user guidelines to determine preferred dsRNA molecules specific for kinesin KSP, as it was known that dsRNA molecules were preferential inhibitory molecules, as evidenced by Tuschl and Khvorova.

Finally, one of ordinary skill in the art would have had a reasonable expectation of success at generating dsRNA molecules because Tuschl et al. taken with Khvorova teach a method of designing a dsRNA and in view of the guidelines it would generate the instant dsRNA molecules as preferable sense to use to target the kinesin KSP target sequence.

Thus, in the absence of evidence to the contrary, the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made.

Applicant's arguments filed 6/24/09 have been fully considered but they are not persuasive.

In response to applicant's argument that the amendment to claim 44 "wherein said KIF11 target sequence comprises a nucleotide sequence of SEQ ID NO: 34" overcomes the 103 rejection, the argument is not found persuasive because the claimed product in claim 44 reads on a double-stranded molecule that targets a KIF11 sequence comprising a nucleotide sequence of SEQ ID NO: 34 which for the reasons set forth above is not obvious over the teaching of Wood et al. taken with Tuschl in further view of Khvorova et al. One of ordinary skill in the art would have been motivated and had a reasonable expectation of success of making and testing siRNA that targets a nucleotide sequence of SEQ ID NO: 34 to determine whether or not it inhibits KIF11 expression. However, in view of the number of possible siRNA molecules that could be produced based on inserting SEQ ID NO: 1 or a nucleotide sequence of SEQ ID NO: 34 into any siRNA algorithm known in the prior art, one of ordinary skill in the art would not have been motivated to select a siRNA molecule consisting of SEQ ID NO: 34 and claims directed to this limitation are not considered obvious over the prior art of record.

Claims 44, 48, and 54-57 are rejected under 35 U.S.C. 103(a) as being unpatentable over Fire et al. (US 6,506,559) taken with Wood et al. (US 6,414,121).

The length of dsRNA molecule is not limited in length because there is no size limitation recited in the instant claims. As pointed out in *In re Mott*, 190 U.S.P.Q. 536 (CCPA 1975), "Claims must be given broadest reasonable construction their language will permit in ex parte prosecution, and applicant who uses broad language runs the risk that others may be able to support the same claim with a different disclosure." Therefore, the claim(s), absent a specific definition set forth in the specification, based on a broadest reasonable interpretation (MPEP 904.01), will be interpreted as a molecule comprising a first and second strand of any length.

Claim 57 is rejected because the phrase “consisting of SEQ ID NO: 34” has been removed from the claim.

With respect to the limitation “wherein said double-stranded molecule, when introduced into a cell expressing a KIF11 gene, inhibits expression of said gene” in the instant claims 44 and 57 and claims dependent therefrom, if a product taught in the prior art has a similar structure to the claimed product, then the product taught in the prior art possesses the characteristics of the claimed product.

> Where the claimed and prior art products are identical or substantially identical in structure or composition, or are produced by identical or substantially identical processes, a prima facie case of either anticipation or obviousness has been established. In re Best, 562 F.2d 1252, 1255, 195 USPQ 430, 433 (CCPA 1977). “When the PTO shows a sound basis for believing that the products of the

applicant and the prior art are the same, the applicant has the burden of showing that they are not." In re Spada, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). See MPEP 2112.01.

Furthermore, since the prior art oligonucleotides meet all the structural limitations of the claims, the prior art oligonucleotides would then be considered to "inhibit expression" of the gene as claimed, absent evidence to the contrary. See, for example, MPEP § 2112, which states "[w]here applicant claims a composition in terms of a function, property or characteristic and the composition of the prior art is the same as that of the claim but the function is not explicitly disclosed by the reference, the examiner may make a rejection under both 35 U.S.C. 102 and 103, expressed as a 102/103 rejection. 'There is nothing inconsistent in concurrent rejections for obviousness under 35 U.S.C. 103 and for anticipation under 35 U.S.C. 102.' In re Best, 562 F.2d 1252, 1255 n.4, 195 USPQ 430, 433 n.4 (CCPA 1977). This same rationale should also apply to product, apparatus, and process claims claimed in terms of function, property or characteristic.

Fire teaches that dsRNA is an improvement over antisense oligonucleotides for inhibiting gene expression (columns 1-4). Fire teaches a vector comprising a construct comprising a promoter operably linked to a nucleotide sequence comprising dsRNA comprising a sense strand and an antisense strand of the target gene (columns 4 and 9). The dsRNA may be formed by a single self-complementary RNA strand or two complementary RNA strands (column 7). A single self-complementary strand would indicate that the vector comprising nucleotides sequences would read on a linker

between the sequences. In such a molecule having several nucleotide sequences, an arbitrary number of nucleotides associated with the inherent hairpin region of the strand can be arbitrarily considered to be a linker that links 25 complementary base pair. This construct could have a linker of one or more strands of the nucleotide sequence containing nucleotide bases on the arbitrary designation of what is, and what is not, the linker sequence. The nucleotide sequence may be 100% identical to the target gene (column 8), which would read on a nucleotide sequence comprising the length of the entire gene. A lipid mediated carrier transport can be used as the vector (column 9). Fire teaches using phagemid clones to produce the RNA (column 18). Fire teaches using phagemid clones to produce the RNA (column 18). However, Fire does not specifically teach targeting RNA of a KIF11 gene.

However, at the time the invention was made, Wood et al. teach antisense molecules targeting kinesin KSP and kinesin KSP being involved in cellular proliferation in cancer (abstract and columns 3-4). Wood et al. further teach a kinesin KSP nucleic acid comprising SEQ ID NO: 34 (SEQ ID NO: 7).

It would have been *prima facie* obvious to a person of ordinary skill in the art at the time the invention was made to combine the teaching of Fire taken with Wood, namely to produce a construct comprising a first strand complementary to a coding region of a KIF11 gene and a second strand that is complementary to the first strand, wherein first strand comprises SEQ ID NO: 34. One of ordinary skill in the art would have been motivated to combine the teaching to study the inhibition of KIF11 expression. "The combination of familiar elements according to known methods is likely

to be obvious when it does no more than yield predictable results." See ***KSR v. Teleflex***, 550 U.S. ___, 127 S. Ct. 1727 (2007).

Therefore the invention as a whole would have been *prima facie* obvious to one ordinary skill in the art at the time the invention was made.

Conclusion

Claims 58 and 61 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brian Whiteman whose telephone number 571-272-0764. The examiner can normally be reached on from 6:30 to 4:00 (Eastern Standard Time). The examiner can also be reached on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor James Douglas Schultz can be reached on 571-272-0763. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Brian Whiteman/
Primary Examiner, Art Unit 1635